IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: McCallester et al. Examiner: S. A. Jiang

Serial No.: 10/092,083

Art Unit: 1617

Filed: March 6, 2003

For: EFFERVESCENT COMPOSITIONS COMPRISING BISPHOSPHONATES AND METHODS RELATED THERETO

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, DC 20231
Sir:

I, Till Rohrich, Ph.D., hereby make the following declaration:

1. I received a Ph.D. degree in Pharmaceutical chemistry from the Albert-Ludwig-University Freiburg (Germany) in the year 1993.

2. After the Ph.D. degree, I was working from 1993 – 2001 in the pharmaceutical industry at the "Institut für Industrielle Pharmazie " in the position "head of galenical development". I have been employed by SwissCo Development AG of Sissein, Switzerland, since December 2001 in the field of effervescent formula development and manufacturing of solid pharmaceutics and food supplements. . My current title is "head of galenical development".

3. I have read the subject patent application, the Examiner's Office action dated June 18, 2003, and prior art cited in support of the rejection: U.S. 5,853,759 (Katdare et al.) and U.S. 5,994,329 (Daifotis et al.). I am fully familiar

with the field of technology embraced by the patent application and the cited prior art.

4. The following experiments were conducted by me or under my direct supervision and control.

The starting pH and buffering capacities of the examples in Katdare et al. and U.S. Daifotis et al. were measured. Acid neutralizing capacity (ANC) per dose of each example was determined according to the method described in USP Official Monographs (301 -attached), only the temperature was different (20°C). The standard procedure was as follows:

5. Sample quantities were measured as stated in the table below and dissolved in 70 ml water at a temperature of 20 ± 3°. 30.0 mL of 1.0 N hydrochloric acid VS was added to the test preparation while stirring. After fifteen minutes accurately measured, titration with acid was begun and, in a period less than an additional five minutes, excess hydrochloric acid was titrated with 0.5 N sodium hydroxide VS to attain a stable (i.e., ten to fifteen seconds) pH of 3.5. The number of mEq of acid consumed was calculated and expressed in terms of mEq of acid consumed per dose. Each mL of 1.0 N hydrochloric acid is equal to 1 mEq of acid consumed.

ANC of Test Formulations According to Patent Descriptions

	Invention				US Patent 5,853,759 (Katdare et al.)				US Patent 5,994,329 (Daifotis et al.)
	Example 2	Example 3	Example 4	Example 5	Example 1	Example 2	Example 3	Example 4	Example 8
Citric acid, mg	1400	420	525	475	650	590	530	600	56.3
Monosodium citrate, mg		1820	1820	1820					
Sodium bicarbonate, mg	800	800	800	800	367	850	850	1500	
Trisodiumcitrate dihydrate, mg									1500
Potassium bicarbonate, mg	694	695	695	695					
Sodium carbonate, mg	160	160	40	80	40	87		40	
Potassiumsodiumtartrate, mg		5	5	5					
Sorbitol, mg	446	450	815	625	47.5	35	190	392.5	
Total weight (dose)	3500	4350	4500	4500	1104.5	1562	1570	2532.5	1556.3
Start pH (dose in 70ml water)	5.7	5.7	5.4	5.5	4.3	6.4	6.1	6.7	6.75
ANC per dose (mEq)	12.6	17.6	14.9	15.7	2.95	9.7	7.8	16.1	6.9

6. Examples 1-4 of Katdare et al. had pH values of 4.3, 6.4, 6.1 and 6.7, respectively. Example 8 of Daifotis et al. had a pH of 6.75. These examples are all outside the claimed pH range of 4.5 to about 5.5.

7. Daifotis et al. Example 8 is not effervescent because it contains no carbonate or bicarbonate component. It is buffered, however, since it contains 1500 mg trisodiumcitrate dihydrate and 56.3 mg citric acid. The measured ANC per dose was 6.9 mEq, making it similar in this respect to Katdare et al. Example 2.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 15.12.03

By: _____
Till Rohrich, Ph.D.

⟨301⟩ ACID-NEUTRALIZING CAPACITY

NOTE — All tests shall be conducted at a temperature of 37 ± 3°.

Standardization of pH Meter — Standardize a pH meter using the 0.05 m potassium biphtha and 0.05 m potassium tetraoxalate standardizing buffers as described under pH ⟨791⟩.

Magnetic Stirrer — Transfer 100 mL of water to a 250-mL beaker containing a 40- × 10-mm magnetic stirring bar that is coated with solid perfluorocarbon and has a spin ring at its center. Adjust the power setting of the magnetic stirrer to produce a stirring rate of 300 ± 30 rpm when stirring bar is centered in the beaker, as determined by a suitable optical tachometer.

Test Preparation —

Powders — Transfer the accurately weighed portion of the substance specified in the individu monograph to a 250-mL beaker, add 70 mL of water, and mix on the *Magnetic Stirrer* for 1 mi

Effervescent Solids — Transfer an accurately weighed quantity, equivalent to the minimum lab dosage, to a 250-mL beaker, add 10 mL of water, and swirl the beaker gently while allowing th reaction to subside. Add another 10 mL of water, and swirl gently. Wash the walls of the beake 50 mL of water, and mix on the *Magnetic Stirrer* for 1 minute.

Suspensions and Other Liquids — Shake the container until the contents are uniform, and determine the density. Transfer an accurately weighed quantity of the uniform mixture, equival the minimum labeled dosage, to a 250-mL beaker, add water to make a total volume of about 7 mL, and mix on the *Magnetic Stirrer* for 1 minute.

Lozenges — Accurately weigh not less than 20 lozenges, and determine the average weight. Select and weigh 2 lozenges, and transfer them to a 250-mL beaker containing 70 mL of water

Nonchewable Tablets — Weigh not less than 20 tablets, and determine the average tablet we Grind the tablets to a fine powder, mix to obtain a uniform mixture, and transfer an accurately weighed quantity of it, equivalent to the minimum labeled dosage, to a 250-mL beaker. If wettin desired, add not more than 5 mL of alcohol (neutralized to an apparent pH of 3.5), and mix to w the specimen thoroughly. Add 70 mL of water, and mix on the *Magnetic Stirrer* for 1 minute.

Chewable Tablets — Prepare as directed for *Nonchewable Tablets*.

Tablets That Are Required To Be Chewed — Transfer 1 Tablet to a 250-mL beaker, add 50 m water, and mix on the *Magnetic Stirrer* for 1 minute.

Capsules — Weigh accurately not less than 20 capsules. Remove the capsule contents completely, with the aid of a cotton swab if necessary. Accurately weigh the empty capsules, a determine the average weight of the contents per capsule. Mix the combined capsule contents

obtain a uniform mixture, and proceed as directed for *Nonchewable Tablets*, beginning with "transfer an accurately weighed quantity of it."

Procedure for Powders, Effervescent Solids, Suspensions and Other Liquids, Lozenges Nonchewable Tablets, Chewable Tablets, and Capsules — Pipet 30.0 mL of 1.0 N hydrochl acid VS into the *Test Preparation* while continuing to stir with the *Magnetic Stirrer*. [NOTE — Where the acid-neutralizing capacity of the specimen under test is greater than 25 mEq, use 6(mL of 1.0 N hydrochloric acid VS.] Stir for 15 minutes, accurately timed, after the addition of t acid, begin to titrate immediately, and in a period not to exceed an additional 5 minutes, titrate excess hydrochloric acid with 0.5 N sodium hydroxide VS to attain a stable (for 10 to 15 secon pH of 3.5. Calculate the number of mEq of acid consumed, and express the result in terms of n of acid consumed per g of the substance tested. Each mL of 1.0 N hydrochloric acid is equal to mEq of acid consumed.

Procedure for Tablets That Are Required To Be Chewed — Pipet 30.0 mL of 1.0 N hydroc acid VS into the *Test Preparation* while continuing to stir with the *Magnetic Stirrer* for 10 minu accurately timed, after the addition of the acid. Discontinue stirring briefly, and without delay re any gum base from the beaker using a long needle. Promptly rinse the needle with 20 mL of w collecting the washing in the beaker, and resume stirring for 5 minutes, accurately timed, then to titrate immediately, and in a period not to exceed an additional 5 minutes, titrate the excess hydrochloric acid with 0.5 N sodium hydroxide VS to attain a stable (for 10 to 15 seconds) pH c Calculate the number of mEq of acid consumed by the Tablet tested. Each mL of 1.0 N hydroc acid is equal to 1 mEq of acid consumed.